Evaluation of Lesion Severity in Transient MCAO Rat Brain During Early Reperfusion Using Combined Cerebral Vascular Reactivity and Diffusion Imaging

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Purpose:
Ischemic stroke is a devastating disease in the United States and causes a heavy burden of the medical care for the entire world. Tremendous effort has been made to detect the lesion and provide the appropriate treatment at an early stage. An example is the use of tissue plasminogen activator (tPA), however, it acts like a double-edged sword—restoring the perfusion early enough can help to save the mild lesion tissues and reperfusion may also help to the secondary cell death. In this study, we aim to propose a simple and noninvasive MRI method to evaluate early stage of reperfusion and determine the potential salvageable tissue in the transient Middle Cerebral Artery Occlusion (MCAO) rat brain.

Material and Methods:
Ten MCAO rats (38±4 g) under 1.5% isoflurane anesthesia were scanned on day 1 after 1-hour MCA occlusion. MRI measurements were performed using a 9.4T/31 cm magnet interfaced with VNMRJ consoles (Varian) and an 1H surface coil (2.8 cm×2 cm). T2-weighted images were acquired with a fast spin-echo sequence (TE=10 ms; TR=3 sec; FOV=2 cm×2 cm; matrix=256×256; thickness=1.0 mm; 8 echo train length). The continuous arterial spin labeling (CASL) CBF calculation follows: CBF = (1−S\text{CBF}−S\text{normo})/(2−S\text{CBF}+S\text{normo})×100 (Eq.1), where S\text{CBF} and S\text{normo} are signal intensity of the image without and with the RF spin labeling respectively. CBF was determined by the arterial spin labeling. Bipolar diffusion gradients in three dimensions were inserted between the RF excitation pulse and data acquisition to obtain diffusion images (TE=14 ms; TR=250 ms; FOV=3.2 cm×3.2 cm; image matrix=128×128; 1 mm thickness). Two b factors (b=1.08×10^7 s·mm^-2) were used for obtaining apparent diffusion coefficient (ADC) maps. The CVR calculation based on ASL follows Eq.2, where CBF\text{normo} and PetCO\text{normo} are the CBF and end-tidal CO2 concentration under normocapnia condition respectively; CBF\text{hyper} and PetCO\text{hyper} are those values under hypercapnia condition. Mild hypercapnia was induced with 6% CO2 inhalation. The rats were sacrificed on day 7 after the occlusion and H&E stained histology was performed. An experienced pathologist carefully delineated the brain regions with damaged neurons.

Results:
Figure 1 shows two continuous coronal images of the T2-weighted images, CBF, ADC, and CVR images in two representative rats scanned on day 1, and the corresponding histology images in the same rat brains sacrificed on day 7 after a 1-hour MCA occlusion. The lesion areas in the right side of MCAO rat brain show hyper-intensity in T2-weighted images involving the sub-cortex and some cortex regions. The behavior of CBF varies from rat to rat, we observed higher baseline CBF in some of the lesion area than the corresponding areas at the control side in some (6 out of 10) of the MCAO rats on day 1 of the occlusion. The ADC decreases in the lesion area in contrast to its homologous control side and the spatial pattern correlates well with the histology lesion areas. The CVR image reveals the extensively impaired vascular response to CO2 and its area exceed all the lesion size shown in the other imaging modalities. The bottom row portrays the schematic lesion zones demarcated by the lesion areas in the CVR, ADC and histology images. Zone 1 (blue) represents the region outside the impaired CBF area but within the lesion side hemisphere; zone 2 (light blue) denotes the compromised CBF region but normal ADC, zone 3 (red) presents the brain region with impaired ADC and CVR, which is consistent with the lesion region in the histology image.

Discussion:
Early detection and proper management of ischemic stroke is crucial to improve the survival rate and reduce the long-term disability. Thrombolytic therapy with early recanalization of occluded cerebral vessels, on the one hand, can help to restore the function of salvageable tissues; on the other hand, reperfusion may also lead to the production of free radicals and toxins, increase microvascular permeability, aggravate edema, increase the risk of hemorrhage and secondary cell death. It is known that the ADC reduction happens in the very early stage of the ischemic region generally considered as a result of cytotoxic edema subsequent to the metabolic energy depletion and the declined volume of extracellular space. Consequently, the lesions with decreased diffusion are usually thought to represent the core of the infarction. Our data is coincidence with this concept, showing consistent spatial pattern between the ADC reduction region and the actual histology lesion delineated by the pathologist on the day 7 of post-occlusion. Interestingly, CBF of the lesion region could appear either higher or lower (rat A in Fig. 1) than the contralateral region, this phenomenon was also observed by other group’s studies and it might be related to the surgery procedure for animal model, the efficiency of recanalization as well as the severity of the ischemic attack. More importantly, a much more extensive area of the declined cerebral vascular reactivity in response to mild hypercapnia was consistently observed after the reperfusion in this study, but these impaired CBF areas with normal ADC seems to be intact in the actual histology images sacrificed on day 7 after the transient ischemic occlusion. It implies that the process of vascular response toward the ischemic attack is rapid and the involved impaired hemodynamic area or volume is much broader than the actual brain lesion area. These findings could potentially help to assess the lesion severity in different brain regions. When combining ADC and CVR images, three zones regarding severity of the lesion can be identified at a relatively early stage (24 hours) of reperfusion: normal brain region zone 1 with the intact ADC and CVR; mild lesion region zone 2 with compromised CVR and intact ADC and severe lesion zone 3 with impaired CVR and ADC (Fig. 1). The existence of zone 2 might be due to the dysfunction of transient vascular response with benign edema ensuing the ischemic attack and reperfusion process, however, its underlying mechanisms needs more thorough investigation. It would be of great importance and very exciting to further explore whether the zone 2 could serve as the prospective treatment target to accelerate the associated pathological progression and improve the clinical outcomes.

Conclusion:
In conclusion, the regions showing impaired cerebral vascular response to mild hypercapnia but with intact ADC correlates well with positive histology outcome, and the spatial pattern of the decreased ADC regions matches well with the histology lesion areas. Therefore, the areas determined by the combined ADC and CVR images are important to evaluate the early stage of reperfusion lesion severity and the mismatched areas with compromised CVR but intact ADC (zone 2) potentially could serve as the treatment target.

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References:

Figure 1 Two continuous coronal brain slices of the T2-weighted images, CBF, ADC and CVR images in two representative rats scanned on day 1, the corresponding histology H.E. images sacrificed on day 7 after 1-hour MCA occlusion and the identified lesion zones determined by CVR, ADC and histology images.